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STANFORD UNIVERSITY SCHOOL OF MEDICINE
Department of Genetics

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Dr. Robert Olby
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Dear Professor Olby,

Thank you for your letter of October 16th and the enclosed chapter. I have taken what time I could during the last few days to digest this and to read Dubos' memoir on Avery, which I succeeded in tracking down to the Royal Society but had overlooked until now. Thank you for bringing this to my attention.

I am a little puzzled that at page 40 Dubos uses the date 1932, twice. If this is not an egregious typographical error I wonder what significance it does have. Do you know the actual period during which Avery was incapacitated between 1928 and 1932? Or was it, in fact, Dawson who thrust the significance of Griffith's finding upon Avery's attention?

I am particularly glad to note your remark about being in California in January and if this is not too long an interval, I think I could discuss your chapter in detail with you much better face to face than by labored written remark. I have very little to add to the detail of what you have put down. I think I do have to say that the general discussion of the biology of bacterial variation may be rather confusing to a reader who is not already familiar with this history. It might have been preferable to preface the entire chapter with a historical review rather than intersperse the critical issues at various points in the chapter. Then, I wonder too if you are not trying to force a theoretical outlook on Griffith to a level of detail that he never had. It seems inappropriate to put the label Lamarckian in a point of view that was not well informed about the nuances of the issue that it presents nor about the elements of related controversy in other fields of biology. Griffith, as I read his papers, seems to have gone out of his way not to produce a general theoretical framework for his experimental findings,and where he unavoidably introduces a phrase here and there of that tenor there is the risk of overinterpreting it. Of course, many bacteriologists had an implicit theory of bacterial biology and it would be useful to try to find the internal evidence that would help make this explicit.

Nevertheless, I think I would have to agree that the background history of bacterial variation is presented in a somewhat confusing way, by being interleaved with the effort to interpret Griffith's theoretical constructs. It would be better, if you wish to go into this in so much detail, to set out a separate chapter, or section, on the general issues of bacterial variation first, for the period from about 1890 to 1928; and then to place Griffith;s thinking in that context.

Even simpler would be a restatement of Griffith's motivation along more phenomenological lines. He had been impressed 1) that R --> S in vivo, and in anti-R antiserum, with certain strains (See his chapter in System of Bacteriology for a succinct account); 2) this 'transformation' occurred with particular readiness with large inocula of R cells, furnishing a nidus -- which brought in the question of the mutual interaction of R (incipient S?) cells with one another, as well as with the host/serum factors; from which he was naturally led to 3) the superiority of S cells even when heat-killed to encourage the transformation; but then surprise ----- 4) transformation from one type to another, as well as reversions of the R to its original type. (The latter, by the way, were also reported to occur in some of Griffith's experiments; but these probably were not gene transfers, but selection of spontaneous reversions like "2)".

What I still do not know is whether Griffith could have been unaware of a long literature on paragglutination. Perhaps this would have been so disreputable, he preferred not to mention it. He should have been well aware, of and much impressed by, Andrewes' and later work on variations in Salmonella. Probably he would have interpreted these as serum-induced effects. But, again, I feel it may be a mistake to take his theory more seriously than he would have defended it himself.

I am glad to see the very fair treatment that you have given to Mirsky's criticism. About the genetic interpretation of transformation I think I would put even more stress on the ambiguity that attached to a phenomenon that had so far been demonstrated only for the synthesis of a capsular polysaccharide. There really was not a shred of evidence that any other aspects of the genetic mechanism of the pneumococcus was involved until Hotchkiss' studies which were reported in 1950-51 and, of course, converged with a variety of other work, including my own, that gave some substance to the idea that bacteria had a system of genes resembling in most respects those of the other organisms upon which post-Mendelian genetics was founded. Few geneticists in 1945 (including myself!) were prepared to take on what seemed like the formidable risks of working with the pneumococcus and the labor that would be involved in assembling the reagents needed to repeat the Avery experiments. Instead, people like Francis Ryan and I were asking whether it might not be possible to obtain a similar result in other microorganisms -- at first pre-eminently Neurospora -- whose genetic system was established beyond doubt. As mentioned in my letter these experiments were, of course, unsuccessful but they did lead to the further steps that you know about.

One pitfall -- the expression "directed mutation" can be used both in a literal and a formal sense and it just is not clear whether Dobzhansky meant that phrase to encompass the possibility of the transfer of a genetic function. The very term" transformation" embraces exactly the same ambiguity. Sometime later I tried to replace it with the term "transduction", intended to have a generic connotation. However, the community of bacterial geneticists would have none of it, and the word came to be confined to the virus-mediated transduction whose discovery had provided the context for the neologism.

I will be covering some of this background in a discussion of the antecedents of my own work on bacterial recombination in a paper that I hope will be ready by the time of your visit. But there probably will not be very much substantially new in it that is not covered, at least hastily, in some of my earlier reviews -- particularly items #13 and 17 in the bibliography of my letter to Nature.

Some of these questions, like the early theories of bacterial heredity, and the meta-problems of the isolation of the disciplines of medical bacteriology and of agricultural and academic genetics would undoubtedly take you rather far afield from the central concerns of your present writing. But when you visit in January perhaps I might persuade you to take an interest in a deeper investigation of the history of the interaction of these disciplines than has been undertaken so far, and to which my own writing would hardly be more than an introduction. This kind of reinterpretation of the early history of this aspect of microbiology should be very timely -- we have learned enough to give a definite structure to the contemporary scientific outlook on these problems; on the other hand I think not too much time has gone by that the task of reconstructing valid if outdated conceptual formulations may not be impossibly difficult.

This letter will also include a few tidbits which I hope are self-explanatory.

Sincerely yours,

Joshua Lederberg
Professor of Genetics

JL/rr
Enclosures

Memo from *To:*

JOSHUA LEDERBERG

P.S. some textual notes

p.53/4 Can you provide a precise date to the 1943 lecture at Rockefeller?

What 'story that Avery was vehemently attacked'?

Source of assertion that Dobzhansky had visited Avery < 1944.

(Question Pollock on:) <u>evidence</u> that Griffith and Avery had never met or corresponded. (What are acceptable standards of proof for such an assertion).

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great, but these things are dangerous when matters are in a qualitative stage.

(Hotchkiss, 1972)

Accordingly we find another footnote in Boivin's Cold Spring Harbor paper which reads:-

> Despite apparently identical experimental conditions, the transformation of R_2 into S_1 through the action of the desoxyribinucleic acid of S_1 is not regularly produced. In a dozen tubes, containing the same volume of medium and the same dosage of desoxyribonucleic acid, inoculated with the same number of bacteria, one frequently finds tubes giving rise to transformation side by side with others where no transformation occurs. The number of bacteria at the beginning and end of the culture and the concentration of the desoxyribonucleic principle do not allow an explanation on statistical grounds of the proportion of positive results obtained in the different experiments. All takes lace as though a factor, still unknown, were able to facilitate or to prevent transformation.
>
> (Boivin, 1947, 8)

To make matters worse other workers had difficulty in repeating Boivin's work, perhaps due to the difference in the competence of different strains (Ravin, 1969, 65). Had Boivin's strains #17 and #24 been available to other workers, perhaps repetition would have been achieved, but these "were lost when the tubes containing the parent strains were broken in a careless accident." (Vendrely, 1972.) Boivin was at the time in hospital following his first serious attack of cancer. "Moreover," wrote Vendrely, "Lederberg, who I believe, had a duplicate of Boivin's collection, also lost these strains. All these

N.B. We had received strains from Boivin but never confirmed his finding. In correspondence with Tatum, he admitted that these might have lost their competence in his own hands, and stated he would try to recover others on which he could verify the transformation himself. His illness supervened. The statement that we lost these strains should not be repeated without this clarification;,it is doubtful that we ever had them.